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10/617,885	07/14/2003	Donald Jeffery Zack	001107.00368	3413

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,885	ZACK ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-9,13-17 and 19-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner prosecuting this case has changed. All inquiries directed to the application should be directed to examiner W. - C. Winston Shen.

This application 10/618,084 filed on July 14, 2003 and claims the benefits of a provisional application 60/395,753 filed on 07/12/2002. Claims 1-9, 13-17, and 19 stand withdrawn as directed to non-elected invention. Claims 20-53 are canceled.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Status of claims: Claims 10-12 and 18 are currently under examination.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 10-12 and 18, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make an/or use the invention for the reasons of record set forth in the office action of Non-Final rejection mailed out on 04/24/06 as reiterated below.

The specification does not reasonably provide enablement for claims directed to a method of preventing neuronal cell death in a mammal comprising administering to said mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker, wherein the nucleic acid molecule can effectively be expressed and/or administering to said mammal a purified human neuronal marker protein to prevent any human disease occasioned by neuronal cell death (e.g., Alzheimer's disease, Parkinson's disease, age- related macular degeneration, spinal cord injury, Huntington's disease, head trauma, neurological disorders).

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention breadth of the claim

The present invention is drawn to a method of preventing neural cell death by administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid

molecule can effectively be expressed and/or administering to said mammal a purified human neuronal marker protein to prevent any human disease associated with neuronal cell death. Although the specification states, "nucleic acids and the corresponding encoded proteins markers of the present invention can be used therapeutically in a variety of modes (p. 61, [49], the specification does not provide any specific and substantial or well-established use comprising administering a nucleic acid molecule expressing a neuronal marker and/or purified neuronal marker of the elected species invention (e.g., NM Mus musculus retinal S antigen) other than through a battery of methods such as non-viral, viral, liposomes, nanospheres for therapeutic preventions.

The claims when given the broadest reasonable interpretation encompass a method of administering a nucleic acid molecule expressing a neuronal marker and/or purified neuronal marker, by any route, wherein the nucleic acid of the composition can effectively be expressed for the intended use of preventing a disease associated with neuronal cell death.

Specific considerations for in *vivo* gene therapeutic transfer such as systemic barriers (e.g., degradation of DNA in plasma, inability of DNA to target specific organs, largely ineffective administration via the oral route) and *cellular DNA barriers* (e.g. endosomal escape of DNA, lysosomal degradation, cytoplasmic stability of DNA, translocation of DNA to the nucleus) have to be addressed for an *in vivo* gene therapy method of preventing a human disorder disease associated with neuronal cell death. As such the specification lacks any description regarding the method (route, vectors types, dosage) of preventing a human disorder disease associated with neuronal cell death therefore, the broad aspects of gene therapy composition to

treat any human disorder having an inflammatory component is not reasonably enable for the full scope embraced by the claims.

The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application.

State of the prior art

The Invention is in the nature of a method of administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed and/or administering a purified neuronal marker protein to prevent any human disease associated with neuronal cell death.

Regarding the claimed invention drawn to a method of administering a composition comprising a non-viral, free DNA vector, for prevention of any type disorder associated by neuronal cell death, Applicant' claims as written encompass a genus of nucleic acid molecules to prevent any human disorder characterized by neuronal cell death. For non-viral gene therapy the specific target of the disease have to be known, since clinical success is empirical and must be determine on a case-by case bases. For example, in the case of an inherited disorder, the insertion of a new gene that ultimately corrects a deficiency requires that the new gene product is present in sufficient amount to achieve a therapy. By contrast, in acquired diseases, since a particular gene or unrelated biochemical process may contribute to the disorder, the approach to therapeutically target a human disorder is complex by the number of factors to be considered and often the incomplete understanding of the pathology of the disease. Besides understanding of

how a mutation leads to a disease, it is important to determine which cells of the body are suitable targets for effective therapy, for examples, disorders resulting from the deficiency of a circulating protein (e.g., clotting factors) may be corrected by expression of the relevant gene in skin or muscle cells, even if the protein is normally made in liver, as long as is secreted into the bloodstream (Orkin et al., Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995, p l 0, paragraph 3). Thus, each therapeutic approach should encompass the specifics for the human disorder being contemplated. Hence the application of gene transfer technology is complex and the ability to develop clinically efficacious therapies is limited by problems that plague all gene therapy strategies (see, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 1996, p.81). Of note, the Marshall reference (Science, 1995,269, pp. 1050-1055,) indicates," there has been no unambiguous evidence that prevention has produced therapeutic benefit (page 1050, column 1). Even data from the pioneering ADA trials are not decisive and "difficulties in getting genes transferred efficiently to target cells, and getting them expressed, remains a nagging problem for the entire field (page 1054, column 3). This problem afflicts all areas of gene therapy (see, p. 1050)." Concurring with Marshall, Verma and Somia (Nature, 1997) state that" the Achilles heel of gene therapy is gene delivery... and thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... [non-viral gene therapy approaches] suffer from poor efficiency of delivery and transient expression of gene" and they go on to say that "although thee are reagents that increase the efficient delivery, transient expression of the transgene is a conceptual hurdle that needs to be addressed" (Nature, 1997, p. 239, col. 2, paragraph 2). The specification is silent about any specific examples for preventing any disorder associated with

neuronal cell death. Hence, it would be undue experimentation for one of ordinary skill in the Art to make and use any type of method to prevent a human disorder associated with neuronal cell death by using a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent said disorder.

In relation to the method of administering composition comprising a non-viral, free DNA vector encoding a gene product comprising a coding sequence for a neuronal marker for the intended use in gene therapy, prior art discloses systemic and intracellular barriers affecting expression of non-viral gene expression constructs. For example, problems related to naked DNA digestion by bloodstream nucleases and deposits of large DNA molecules in the first capillary bed encountered after intravenous injection (diverting complexes injected into organs, to enable their circulation) can be reduced by condensing the DNA with polycationic chitosan (Brown MD, Int J Pharm, p. 4, col. 2, paragraph 3). Though the Art has developed strategies to overcome extracellular systemic barriers, the Art also recognizes the importance of studying gene therapy in the context of a specific disease since it was found that even gene transfer to the lung epithelium is severely limited by purulent infective sputum, a normal feature of cystic fibrosis lung, and by normal mucus (Brown et al., p. 13, col. 1, paragraph 1). In relation to intracellular barriers, the synthetic gene-transfer complexes face several obstacles to reach the cell nucleus for transcription of the delivered DNA. After internalization by receptor-mediated or adsorptive endocytosis, the complex is enclosed within the endosomal or lysosomal membrane, and therefore separated from the cytoplasm. A combination of both endosomal disrupting peptides and receptor mediated uptake have been used in complexes to facilitate the endosomal barrier and specific cell uptake, however all these strategies have enjoyed moderated success

(Brown, p. 13, col. 1, paragraph 2). The inability to achieve effective gene transfer in differentiated; non- dividing cells possessing an intact nuclear membrane may pose the most important limitation for successful nonviral gene transfer (Zabner et al., JBC, 270, 18997-19007, 1995, p. 19005, col. 2, paragraph 1 and 2). Lechardeur et al. described metabolic instability of plasmid DNA in the cytosol as a further barrier to gene transfer (Gene Ther. 6:482-497, 1999). Hence, one skilled in the Art at the time of the invention could not reasonably predict the use of any method of administering, by any route, a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent a disorder associated with neuronal cell death.

In so far as to the claimed invention drawn to a method of administering a composition Comprising viral vectors, for prevention of any type disorder associated by neuronal cell death, Applicant' claims as written encompass a genus of nucleic acid molecules to prevent any human disorder characterized by neuronal cell death. However, the prior art would deem such unspecified methods and/or steps for preventing any human disorder characterized by neuronal cell death as unpredictable. The following is the state of the prior art regarding the use of viral vector such adenovirus vectors: Tjuvajev et al. (Cancer Research 1999 vol.59 p.5186-5193) teach that increasing Ad does beyond a certain threshold may result in greater biliary and hepatic toxicity compared with therapeutic effect and that optimization of new ad vector regarding optimal dose and timing during treatment is important (see p. 5192 2nd column, 1st and 2nd ¶). In addition, issues regarding pre-existing immunity towards still plague the use of adenovirus vectors as therapy complicating the outcome. Bramson et al (Gene therapy 1997, 4 1069-1076) teach that continued preclinical experimentation regarding this issue is necessary and yield

improved treatment strategies that can be applied effectively in a clinical setting (see p. 1074 1st ¶). Yu et al. further teach that rapid increased pools of cytokines may lead to dysfunction and damage of multiple organs (See p. 1 3rd column 1st ¶). At time of the invention, Thomas et al. (Nature 2003 volume 4 p. 346-358) teach that Jesse Gelsinger death was due to massive inflammatory response that led to disseminated intravascular coagulation, acute respiratory distress and multi-organ failure due to the systemic delivery of ad vector (see p. 347 Box 1 2nd ¶ 2).

In relation to the method of administering composition comprising a purified human neuronal marker protein a coding use therapy, prior art discloses systemic and intracellular barriers affecting the use of recombinant protein. For example, Shah et al (Advances in Genetics 2005 Vol 54 p. 339-361) teaches the major issues with use of therapeutic proteins are the following 1) delivery to desired sites 2) the dose of the protein that needs to be administered in order to engender a desirable biological effect may also result in an increase in adverse events and 3) recombinant proteins have a short half-life in the circulation because of circulating proteases, and therefore, the half-life is limited (see p. 343 2nd ¶).

At best, the state of prior art with use of either non-viral or viral vectors expressing neuronal markers and/or the use of purified protein of neuronal markers for prevention of neuronal cell death is unpredictable and required one skilled in the art undue efforts in experimentation. Hence, one skilled in the Art at the time of the invention could not reasonably predict the use of any method of administering, by any route, a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent a disorder associated with neuronal cell death.

Insofar as the Prevention of neuronal cell death in a mammal, the claims when given the broadest possible interpretation encompasses any neuronal disease of the nervous system, from neurodegerative diseases, such as Alzheimer's disease (AD) and stroke, to severe psychosocial trauma (Koliatsos et al., 1999, Cell death and disease of the nervous system, p. 549, paragraph 2). Boxer et al., discloses that mechanisms involved in producing cell death involved activation or blockade of cell-surface receptors and/or intracellular targets. The regulation of extrinsic and intrinsic mechanisms leading to neuronal cell death is present in two distinct pathways, the traditional one of necrotic cell death and a second one, by apoptosis or programmed cell death (PCD) (Boxer et al., 1997, Drug Discovery Today, p. 219, col. 2 and p. 221, Fig. 1).

Regarding activation or blockade of cell surface receptors, there is overwhelming evidence in the Art supporting that excitatory amino acid (EAA) receptors can induce selective neuronal death both, in vitro and in vivo. EAAs is one of the factors contributing to necrotic cell death that is due to ischemia, traumatic brain injury, hypoglycemia, and epileptic seizures, though it is unlikely that glutamate receptor activation is the major etiological factors in specific chronic neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration) (Boxer et al., 1997, Drug Discovery Today, p. 222, col. 1 paragraph 2). Application of EAA on neurons causes an increase in intracellular calcium. The mechanism by which "calcium overload" induces cell death has not been completely elucidated (Boxer et al., 1997, Drug Discovery Today, p. 222, col. 2 paragraph 2). Drug therapy that involved the use of blockers to the three classes of ionotropic receptors (e.g., linked to an ion channels) of EAA (e.g., NMDA, AMPA, and Kainate receptors) and other therapies to reduce release of Ca++ from

intracellular stores is an on going process providing conflicting treatment results (Boxer et al., 1997, p. 224, col. 1, last paragraph bridging to col. 2 paragraph 1).

In relation to intracellular targets, several intracellular targets for neuronal protection such as calpain inhibitors, blockage of nitric oxide (NO) and scavenge of reactive oxygen species have been considered in the Art. Calpain are proteases activated only by high levels of calcium and they target structural proteins. Boxer teaches (1997, p. 224, col. 2, last paragraph) that calpain inhibitors are perhaps the most attractive intracellular target for neuronal protection, however a mayor limitation of this type of strategy is that' once high levels of intracellular calcium have occurred, a variety of parallel pathways are activate". Similarly, the blockage of NO, which has been shown to be cytotoxic and activated by elevated intracellular calcium, is not specific to the brain and also inhibits endothelial NO, which produces undesirable effects on systemic blood pressure and cerebral flow (Boxer, 1997, p. 225, col. 1, paragraph 2). Boxer discloses (1997, p. 225, col. 2, paragraph 2), oxidative damage as a mechanism contributing to etiology of chronic degenerative diseases, specifically in AD wherein overproduction of β-amyloid may kill neurons via generation of reactive oxygen species. Mitochondria dysfunction may also contribute to the pathogenesis of chronic neurodegenerative disorder by chronic poisoning of the oxidative phosphorylation pathway, decreasing production of ATP and ultimately producing pathologies seen in Huntington's disease and Parkinsonism. Thus antioxidants such as vitamin E, β-carotene and vitamin A may be potential as prophylactic prevention to relieve oxidative stress. Transforming growth factor-β1 also protect neurons in culture against both calcium and free radical-mediated degeneration via preservation of mitochondrial potential and function. Similarly, neurotropic factors (e.g., nerve growth factor,

basic fibroblast, brain-derived neurotropic factor) attenuate glutamate-induced peroxides and increase antioxidant enzymes and thus protect cells from oxidative stress (Boxer, p. 226, col. 1, paragraph 1). However, factual data about specificities of neurotropic factors in adult CNS have not been well work out (Schwab, Science, 2002, Repairing the injured spinal cord, p. 1030, col. 2, paragraph 2). Schwab teaches that "the regenerative effects of nerve growth factor on peripheral nerves, for example, have turned our to be clinically useless because nerve growth factor affects pain-sensitive neurons, resulting in hyperalgesia (increase sensitivity to pain). Although more that 30 neurotropic factors are known, fewer than six of them have been investigated as potential preventions for lesioned spinal cord in animal models". Similar insight into the unpredictability for neuronal protection is provided by Boxer when he teaches that progressive degenerative diseases may all result form an inability of the brain to prevent free radical damage or oxidative stress (p. 226, col. 1, paragraph 1).

In so far as programmed cell death (PCD), an inappropriate activation of apoptosis may lead to pathologies related to stroke, Ad, AIDS dementia and aging (Boxer, p. 226, col. 2, paragraph 2). Recently, a cascade of events involved in activation of extracellular and intracellular pathways leading to cell death has disclosed a new family of proteases, caspases (Davis, 2001, Current Opinions in Investigational Drugs). Caspases are proteolytically activated from an inactive proenzyme or zymogene stage, by mechanisms that involved extrinsic and intrinsic cellular pathways regulating maturation of caspase 8 and caspase 9, respectively. Substrates for the effectors of caspases are plentiful, including many proteins associated with the pathology of neurodegenerative disorders (Davis, 2001, p. 655, col. 2), Such as the protein associated with Kennedy's disease, androgen receptor. Moreover, Davis teaches that "the precise

mechanism by which the caspases cleavage of these substrates contributes to the cell process is not known, although several of these cleaved proteins have been shown to cause the death of cells and to increase the sensitivity of cells to other death stimuli" (p. 656, col. 1, paragraph 1). Davis anticipates that caspase cleavage of the holoprotein substrate might cause a loss of a protective function; indeed, some of the substrates have been reported to exhibit anti-apoptotic properties (Davis, 2001, p. 655, col. 2).

Hence, molecular mechanisms in neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, Huntington's disease) more likely to mediated cell death process, appears to involve a highly regulated, pleiotropic cascade of events (Davis, Current Opinion in Investigational Drugs, p. 654, col. 2, last paragraph). As neuronal cell death is unlikely to have a single, discrete pathway, one skilled in the Art at the time of the invention could not reasonably predict the use of a method of administering nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent a neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, Huntington's disease).

Insofar as the extrapolation of results from the animal model to the human model, prior Art teaches that the conditions of a particular disease in an animal model may not correspond with the human condition. For example, mice with mutations in the cystofibrosis gene do not exhibit the pulmonary effects of cystic fibrosis seen in man, but rather suffer from severe gastrointestinal obstruction (Orkin et al., Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, December 7, 1995, p. 11 paragraph. 3). Thus, the relevance of animal models for prevention of human neurodegenerative diseases may be

compromised by phenotypical difference between the human patient and animal models of the disease. Thus, the state of prior Art teaches a lack of nexus between animal models to the human model.

Hence, one skill in the Art at the time of the invention could not reasonably predict the use of any nonviral or viral vector nucleic acid molecule expressing a neuronal marker and/or the use of purified neuronal marker by any route of administration for prevention of neurodegenerative diseases. Further, a detailed study of the different non-viral gene transfer systems is required in relation to the systemic and intracellular barriers for expression of the therapeutic protein of interest. Brown et al., (2001) conclude that "It is unlikely that a gene delivery system will emerge which has universal applicability and the first license gene therapeutics will utilize a gene delivery system which has been tailored to give high levels of gene expression when administered to treat a specific disease".

The predictability or lack thereof in the art

The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art.

Guidance in the Specification and working examples

Applicant is silent about any factual data of any method of administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be

expressed to prevent neurodegenerative diseases. Moreover, the Applicant is silent in regards to the methods, protocols or steps of isolating NM Mus musculus S antigen from cells and or animals such that a transgenic animal could possibly made; there are no description of any vectors. In addition, the presences of unpredictability regarding claimed methods necessitate working examples and guidance, which are lacking.

Level of Skill in the Art

The relative skill of those in the art is considered to be relatively high at the time the invention was made.

Analysis of Quantity of Experimentation

In relation to the use of non-viral gene transfer technology for prevention of any human neuronal cell death, the Art of record teach that non-viral gene therapy involves complex issues and the ability to develop clinically efficacious therapies is limited by problems that plague all gene therapy strategies. Prior Art teaches the challenges faced in clinical applications of non-viral gene therapy and the need to use a gene delivery tailored as required by the clinical target. Part of the transient expression is attributed to the inability of naked DNA to successfully address the problem of endosomolytic destruction and nuclear entry into differentiated non-dividing or slowly dividing cells. While viral vectors have evolved specific mechanisms for release of viral DNA from endosomes, and mechanisms to gain entry across the nuclear pore complexes, the inability to overcome these limitations for successful nonviral gene transfer requires further developing and testing of the nonviral vectors. Hence, issues such as targeting, endosomolytic release, cytoplasmic stability and nuclear entry have to be addressed for a successful gene expression and prevention with nonviral therapy. Additional, viral vector gene

transfer for prevention of any human neuronal cell death is marred with unpredictability regarding delivery, insertional mutagenesis effects, unpredictability of phenotypes and effects. Hence, experimentation regarding these issues is still needed in the field.

With respect to the prevention of neuronal cell death, the art of record teaches the need for a better understanding of the pathology molecular mechanisms in neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, Huntington's disease) since cell death process appears to involved a highly regulated, pleiotropic cascade of events. A reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification as filed. Without sufficient guidance, the mere enumeration of preventing a human disorder associated with neuronal cell death in the claims is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. Applicants disclose no other details in the as-filed specification in relation to a method a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule expressed in sufficient levels to prevent neuronal cell death. Hence, the scope of the patent protection sought by the Applicant as defined by the claim fails to correlate with the scope of enabling disclosure set forth in the specification.

With regard to the correlation of an animal model with a human gene therapy model, the Art does not recognize a nexus between the animal model, and the prevention of neural cell death. The working examples presented share no nexus with the attainment of clinically efficacious transgene levels. Moreover, it is unclear how by comparing the fight and left eye of a rat of the elected species neuronal marker relates to prevention of neuronal cell death, the specification does not teach how to select or use any neuronal marker, nor does it disclose what

properties of neuronal markers are desirable for use in the methods of the claimed invention. Hence, due to differences cellular environments between the *in vivo* eye expression in an animal model in comparison to the various cell types to which the protein encoded by the nucleic acid of the administered molecule expressing a neuronal is exposed to when it is administered into a human environment, there is no evidence that the behavior of the expressed gene in the in vivo animal model would be predictive of the behavior of the protein in a human model. Hence, one of skill in the art will not find it reasonably predictable how said *in vivo* animal model results could be extrapolated to a human environment without undue experimentation.

As such, and to the extent that the claimed invention is drawn to the methods of a method of preventing neuronal cell death in a mammal comprising administering to said mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent any human disease occasioned by neuronal cell death (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, spinal cord injury, Huntington's disease, head trauma, neurological disorders, the as-filed application does not provide sufficient guidance and/or working examples for a skilled artisan to reasonably enable the claim invention. Due to the large quantity of experimentation necessary to generate the infinite number of derivative as recite in claims 10 and dependent claims 12 and 18 and subsequent screening for selection of any methods a of preventing neuronal cell death by administering a nucleic acid molecule comprising a coding sequence for a neuronal marker, by any route, for the intended use of in vivo prevention any type of human disorder associated with neuronal cell death, one skilled in the Art will have to perform extensive experimentation with

each of these parameters to find the embodiments embraced by Applicant' claims, and as such, this experimentation would be considered undue.

Response to Arguments

The previous office action identified the following issues of record: **(1)** the specification does not provide any specific and substantial or well-established use comprising administering a nucleic acid molecule expressing a neuronal marker and/or purified neuronal marker of the elected species invention (e.g., NM Mus musculus retinal S antigen) other than through a battery of methods such as non-viral, viral, liposomes, nanospheres for therapeutic preventions (See page 4, second paragraph); **(2)** the specification lacks any description regarding the method (route, vectors types, dosage) of preventing a human disorder disease associated with neuronal cell death therefore, the broad aspects of gene therapy composition to treat any human disorder having an inflammatory component is not reasonably enable for the full scope embraced by the claims (See page 5, first paragraph); **(3)** each therapeutic approach should encompass the specifics for the human disorder being contemplated. Hence the application of gene transfer technology is complex and the ability to develop clinically efficacious therapies is limited by problems that plague all gene therapy strategies (See page 6); **(4)** The specification is silent about any specific examples for preventing any disorder associated with neuronal cell death. Hence, it would be undue experimentation for one of ordinary skill in the Art to make and use any type of method to prevent a human disorder associated with neuronal cell death by using a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent said disorder (See page 7, first paragraph); **(5)** The inability to achieve

effective gene transfer in differentiated; non- dividing cells possessing an intact nuclear membrane may pose the most important limitation for successful nonviral gene transfer (See page 8, first paragraph); **(6)** Applicant' claims as written encompass a genus of nucleic acid molecules to prevent any human disorder characterized by neuronal cell death. However, the prior art would deem such unspecified methods and/or steps for preventing any human disorder characterized by neuronal cell death as unpredictable (See page 8, second paragraph); **(7)** At time of the invention, Thomas et al. (Nature 2003 volume 4 p. 346-358) teach that Jesse Gelsinger death was due to massive inflammatory response that led to disseminated intravascular coagulation, acute respiratory distress and multi-organ failure due to the systemic delivery of ad vector (see p. 347 Box 1 2nd ¶ 2) (See page 9, first paragraph); **(8)** Shah et al (Advances in Genetics 2005 Vol 54 p. 339-361) teaches the major issues with use of therapeutic proteins are the following 1) delivery to desired sites 2) the dose of the protein that needs to be administered in order to engender a desirable biological effect may also result in an increase in adverse events and 3) recombinant proteins have a short half-life in the circulation because of circulating proteases, and therefore, the half-life is limited (see p. 343 2nd ¶) (See page 9, second paragraph); **(9)** The regulation of extrinsic and intrinsic mechanisms leading to neuronal cell death is present in two distinct pathways, the traditional one of necrotic cell death and a second one, by apoptosis or programmed cell death (PCD) (Boxer et al., 1997, Drug Discovery Today, p. 219, col. 2 and p. 221, Fig. 1) (See page 10, second paragraph); **(10)** molecular mechanisms in neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, Huntington's disease) more likely to mediated cell death process, appears to involve a highly regulated, plei[o]tropic cascade of events (Davis, Current Opinion in

Investigational Drugs, p. 654, col. 2, last paragraph). As neuronal cell death is unlikely to have a single, discrete pathway, one skilled in the Art at the time of the invention could not reasonably predict the use of a method of administering nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent a neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, Huntington's disease) (See page 13, second paragraph); **(11)** Insofar as the extrapolation of results from the animal model to the human model, prior Art teaches that the conditions of a particular disease in an animal model may not correspond with the human condition. The relevance of animal models for prevention of human neurodegenerative diseases may be compromised by phenotypical difference between the human patient and animal models of the disease. Thus, the state of prior Art teaches a lack of nexus between animal models to the human model (See page 14, first paragraph); **(12)** Brown et al., (2001) conclude that "It is unlikely that a gene delivery system will emerge which has universal applicability and the first license gene therapeutics will utilize a gene delivery system which has been tailored to give high levels of gene expression when administered to treat a specific disease" (See page 14, second paragraph); **(13)** Applicant is silent about any factual data of any method of administering a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule can effectively be expressed to prevent neurodegenerative diseases. Moreover, the Applicant is silent in regards to the methods, protocols or steps of isolating NM Mus musculus S antigen from cells and or animals such that a transgenic animal could possibly made; there are no description of any vectors. In addition, the presences of unpredictability regarding claimed methods necessitate working examples and guidance, which are lacking. (See page 15, second paragraph); **(14)**

Hence, issues such as targeting, endosomolytic release, cytoplasmic stability and nuclear entry have to be addressed for a successful gene expression and prevention with nonviral therapy. Additional, viral vector gene transfer for prevention of any human neuronal cell death is marred with unpredictability regarding delivery, insertional mutagenesis effects, unpredictability of phenotypes and effects. Hence, experimentation regarding these issues is still needed in the field (See page 16, first paragraph); **(15)** Applicants disclose no other details in the as-filed specification in relation to a method a nucleic acid molecule expressing a neuronal marker, wherein the nucleic acid molecule expressed in sufficient levels to prevent neuronal cell death. Hence, the scope of the patent protection sought by the Applicant as defined by the claim fails to correlate with the scope of enabling disclosure set forth in the specification (See pages 16-17, bridging paragraph); and **(16)** The working examples presented share no nexus with the attainment of clinically efficacious transgene levels. Moreover, it is unclear how by comparing the fight and left eye of a rat of the elected species neuronal marker relates to prevention of neuronal cell death, the specification does not teach how to select or use any neuronal marker, nor does it disclose what properties of neuronal markers are desirable for use in the methods of the claimed invention (See page 17, second paragraph).

Applicant's arguments filed on 07/5/06 have been fully considered but they are not persuasive.

Applicants argued that the state of the art of gene therapy in 1995-1999 is not relevant to whether the claimed method was enabled at this applicant's July 13, 2003 priority date. It is the state of art in July 2003 that is relevant to the enablement of claims 10-12 and 18 (Remark, page

18). The applicants recited references listed on the Information Disclosure Statement as evidence that those skilled in the art in July 2003 were able to effectively transfer and express exogenous genes in neurons in *vivo* (page 18) and effectively administer proteins to reduce or prevent neuronal death *in vivo* (page 20).

Response: Previous office action cited broad spectrum of references relevant to enablement and written description issues not only covering 1995-1999 but also reference close to the filing date (See for example, Thomas et al. (Nature 2003 volume 4 p. 346-358, #(7) issue identified of record in the beginning of this section) as well as references post-filing date (Shah et al (Advances in Genetics 2005 Vol 54 p. 339-361), #(8) issue identified of record in the beginning of this section)

Applicants further argued that in determining enablement, the U.S. Patent and Trademark should not be concerned with demonstrations of therapeutic success (Remark, p21).

Response: It is noted that for a therapy claim to be enabled, there has to be evidence of therapeutic effect. While USPTO does not require data from clinical trials, the evidence of therapy is required to support enabling disclosure.

Applicants further argued that understanding the mechanism by which any particular neuronal marker protein reduces neuronal cell death is neither relevant nor required for enablement (Remark, page 22).

Response: While the mechanism *per se* by which any particular neuronal marker protein reduces neuronal cell death is not the concern for enablement, relationship of a gene to a disease

is required for an artisan to have treated said disease with said polynucleotide. The changes of gene expression profile observed by microarray data between wild type and diseased/treated mammals may represent effects that could not be related to the gene whose expression profile is altered. Such changes could be due to other genes downstream or upstream in a pathway and this may represent primary, secondary or tertiary effects. Even in the case of primary effect, it would be case-by-case determination whether administration of nucleic acid encoding a gene can reduce neuronal cell death as claimed. Related statement has been of the record in the previous office action "each therapeutic approach should encompass the specifics for the human disorder being contemplated. Hence the application of gene transfer technology is complex and the ability to develop clinically efficacious therapies is limited by problems that plague all gene therapy strategies (page 6)" (See #(3) issue identified of record in the beginning of this section).

Applicants further argued that even if routine experimentation were required to optimize the claimed methods, that does not make the experimentation undue (Remark, p22); and (5) working examples are not required to enable an invention (Remark, p23).

Response: As discussed in the office action, the state of art of gene therapy was unpredictable at the time of invention. Experimentation required would not have been routine. Since gene therapy was not routine at the time of invention, an artisan would have required specific guidance to practice claimed method and the specification does not provide any specific guidance. Therefore, based on the unpredictability of the process and case-by-case nature of treatment, demonstration of working examples is necessary to convey the enabling nature of the invention as broadly claimed.

It is noted that while applicants have amended their claims, they have not provided substantive arguments addressing the outstanding issues raised in the previous office action. Furthermore, the amended claims continue to encompass administering to the mammal a nucleic acid molecule comprising a coding sequence for any of the neuronal marker protein listed in claims 10 and 11.

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

3. No claim is allowed.

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30

PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Ram Shukla, can be reached on (571) 272-0735. The fax number for TC 1600 is (571) 273-8300. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER